Common Variable Immunodeficiency – Co-morbid Conditions

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Mark Ballow: Disclosures
• I have a financial relationship or interest related to the content of this CME program with the following entities:
  – Talecris Biotherapeutics – advisory board
  – CSL Behring - advisory board
  – Baxter – advisory board
  – Grifols – PI phase 4 IVIG study; consultant
• Unlabeled or investigational products will not be discussed

Learning Objectives
At the conclusion of this session, the participant should be able to:

Become aware of how therapeutic decisions will affect the management of patients with CVID over the course of their lifetime.

Make more effective treatment decisions when managing complications in patients with CVID.
Common Variable Immunodeficiency (CVID)

- Recurrent sinopulmonary infections with encapsulated organisms
- Most common B-cell immune deficiency
  - 1:25,000 to 1:50,000
- Variable onset of clinical findings
  - Often delayed diagnosis by 6-8 yrs
- Low serum IgG, IgA, IgM
  - At least 2 Ig isotypes that are >2 SD below normal for age
  - Poor or absent specific antibody production
- Diagnosis after age 4 to exclude transient delayed hypogammaglobulinemia of infancy (THI)
- Most common PIDD requiring therapy (IVIG)
- 50% share a common HLA haplotype
- Families have individuals with both CVID and IgA deficiency
- Immunologically heterogeneous disorder

Clinical Findings in CVID

- Recurrent sinopulmonary tract infections (73%)
  - Encapsulated organisms
  - Mycoplasma
- Recurrent GI symptoms, chronic GI infection
  - Campylobacter/Salmonella
  - 10% liver disease
- 1/3 develop lymphoproliferative disorder.
  - Intestinal nodular lymphoid hyperplasia
  - Splenomegaly
- Autoimmunity (~25%): RA, celiac disease, ITP, AIHA, systemic rheumatic disease
- Subgroup of CVID have defects in T-cell function
- Increased incidence of lymphoma (NHL) and gastric cancer

Medical Complications in Patients With CVID

- Infections
  - 37%
- Lymphoma
  - 51%
- Nodules in mucosa (oral, nasal, conjunctivae)
- Celiac disease
  - 10%
- Myasthenia gravis
  - 5%
- Diffuse or segmental disorders of the intestines (ulcers, strictures, stenosis, pseudocysts)
- Granulomas in any site
  - 5%
- Hypogammaglobulinemia
  - 2%

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Complications Associated With CVID

Chapel H, Cunningham-Rundles C, et al. [2009].

Chronic Diarrhea in a 32-year-old Woman

Gastrointestinal Issues

- Survey of 248 CVID patients – 21% had significant GI disease
  - Often present with chronic diarrhea and malabsorption
  - Liver disease in 12%
    - Biliary cirrhosis
    - Autoimmune hepatitis
    - Nodular regenerative hyperplasia – portal hypertension and cholestasis
  - Overgrowth of small bowel with pathogens
    - Giardia lamblia
    - Yersinia, Campylobacter, C. difficile, Salmonella
    - Chronic viral enteritis
      - Enteroviruses
      - CMV
  - Autoimmune GI problems
    - Celiac
    - Inflammatory bowel disease

Gastrointestinal Management

- No lake swimming (Giardia lamblia)
- Stool studies
  - Releasing substances – lactose intolerance
  - Cultures – request special cultures for Yersinia/Campylobacter
  - O&P
- Liver function tests
- GI procedures
  - Imaging
  - Xray
  - Endoscopy
  - Biopsies
    - Celiac disease
    - IBD
- Nutrition support
  - Diet
  - Vitamins

Pulmonary Findings in CVID

- Bronchitis/bronchiectasis
  - Serum IgG level at diagnosis does not predict subsequent pneumonias or bronchiectasis
- Granulomatous lung disease
  - 8%-12% of patients
  - May be diagnosed years before the hypogammobulinemia
    - Well-formed, non-caseating granuloma with epitheloid giant cells
    - Often misdiagnosed as sarcoid
  - Lung (54%); lymph nodes and spleen (43%); liver (32%)
  - Autoimmune disorders are commonly associated (54%)
    - Autoimmune thrombocytopenia, hemolytic anemia most common
    - Have low number of switched memory B cells

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Pulmonary Findings in CVID (cont’d)

- Lymphoid interstitial pneumonia (LIP)
  - Lymphoma
- Granulomatous lymphocytic interstitial lung disease (GLILD)
  - HHV8
  - Poorer prognosis, T-cell deficiency, B-cell lymphoproliferative disease
    - Median survival: 13.7 yrs vs. 28.8 yrs
    - MALT

Pulmonary Disease Management

- Baseline high-resolution chest CT
  - Chest x-rays
  - Spirometry
- If lung disease present:
  - Sputum cultures/sensitivities
  - Spirometry – DLCO
  - Pulmonary care
  - Biopsies
    - Flow cytometry
    - Clonality for MALT

Pulmonary Disease Management (cont’d)

- Therapy
  - Bronchiectasis
  - Adequate IVIG/SCIG replacement therapy
  - Prophylactic antibiotics
  - Pulmonary toilet
  - Granulomatous disease
    - Oral steroids/inhaled corticosteroids
    - Hydroxychloroquine
    - TNF inhibitors

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Common Variable Immunodeficiency – Co-‐morbid conditions that effect long term survival

Clinical Findings in CVID: Autoimmune Disease

- Approximately 20%-30% have autoimmune disease
  - Diminished switched memory B cells
- Most common hematologic (11%)
  - Rx IVIG/steroids
  - Rituximab
  - Avoid splenectomy
  - Rheumatologic
  - Endocrine
  - Pernicious anemia
  - Secondary neurologic deficits – B12 deficiency

Lymphoid Tissues

- Lymphoid hyperplasia (20%) – Secondary cytopenias – Evans syndrome
  - Cervical, mediastinal, abdominal
  - Splenomegaly
  - Reactive lymphoid hyperplasia
  - Granulomatous disease
  - Rule out lymphoma – Flow cytometry for tumor markers
  - Clonality by molecular analysis
  - EBV genome

- Hepatosplenomegaly

Cancer: Clinical Findings in CVID

- Malignancies
  - 2%-8% Non-Hodgkin lymphoma
  - More common in the 4th-7th decade of life
  - Female preponderance
  - B-cell type, EBV negative
  - Location in mucosal regions (marginal zone)
  - Associated with lymphoid hyperplasia, granulomatous disease, and elevated serum IgM
  - Gastric cancer

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**Immune Defects in CVID: a Heterogeneous Disorder**

- **T-cell defects**
  - Decreased activation and proliferation
  - Reduced numbers of peripheral blood T-cell subsets
  - Impaired cytokine production
  - Reduced expression of CD40L
  - Increased immunoregulatory T-cells
- **B-cell defects**
  - Reduced number of circulating B-cells
  - Defective up-regulation of CD86
  - Reduced somatic hypermutations
  - Lack of class-switched memory B-cells

**Clinical Phenotypes and Biomarkers**

- **Clinical biomarkers**
  - Poor T-cell function
  - Low B-cell numbers
  - Switched memory B cells
  - Reduced Treg
  - Very low CD21⁺ B cells
  - High serum levels of BAFF and APRIL
- **Genetic markers**
  - Heterozygous mutations/polymorphisms in TNFRSF13B (TACI)
  - Develop autoimmunity and lymphoid hyperplasia

**Switched Memory B-cells in CVID**

- **Switched memory B-cells**
  - CD27⁺ IgM⁻ IgD⁻
  - Group I ≤0.4% vs. group II >0.4%
- **Patients with higher numbers (Group II) of switched memory B-cells** had higher serum levels of immunoglobulins and better antibody responses to pneumococcal vaccine
- **Patients in group I with low class switch memory B-cell** had more autoimmune disease
  - Poorer antibody production to polysaccharide antigens
  - More bacterial pneumonias and bronchiectasis

References:
Common Variable Immunodeficiency – Co-morbid conditions that affect long term survival

Flow Cytometric Evaluation -CVID

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Gene Defects in Common Variable Immune Deficiency (CVID)

- Recent findings have identified specific B cell and T cell genetic defects associated with CVID
  - TACI (Transmembrane Activator and CAML Inducer) deficiency: ~10% CVID
  - BAFF B-cell Activating Factor receptor deficiency: uncommon
  - CD9 deficiency: uncommon
  - ICOS (Inducible COStimulator of activated T cells) deficiency
    - impaired T cell help (uncommon)

Survival Curve for Patients With CVID 1973 to 1998

Survival Curve for Patients With CVID 1973 to 1998

FIG 1. Average decline in FEV1 (% predicted) for PIDs (total group), CVID, and XLA

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Survival in Patients With CVID

Survival (as % of patients with CVIDs, with or without disease related complications, compared with UK general population controls)

Time since diagnosis (UK controls; corrected for median age at diagnosis of cohort [35 years])

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